Review

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Gut-Liver Axis: Modulating the Gut Microbiota and Its Metabolic Products as a Potential Therapeutic Strategy for the Treatment of Hepatic Ischemia-Reperfusion Injury

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Hepatic ischemia-reperfusion injury (HIRI) is a major complication reported in various clinical scenarios such as liver transplantation (LTx), hepatectomy, and acute hepatic insult. This condition affects the restoration of hepatic functionalities post-LTx. Contemporary scientific inquiries have highlighted the involvement of intestinal microbiota and their metabolic by-products in the initiation and progression of HIRI. Perturbations in the gut microbiome, instigated by external stressors such as inflammatory processes, ischemic conditions, and reperfusion events, affect the biosynthesis of metabolites such as short-chain fatty acids (SCFAs), bile acids (BAs), and lipopolysaccharides (LPS). SCFAs can exert anti-inflammatory effects, modulate cellular apoptosis, and attenuate oxidative stress, thereby ameliorating hepatic injury. Other studies have shown that the intestinal microbiota confers hepatoprotective effects by modulating the host's immune response and synthesis of cytokines, controlling inflammation, and enhancing liver protection. This review comprehensively describes the mechanisms underlying the association of gut microbiota and its metabolites with hepatic disease and ischemia-reperfusion injury. The findings from recent studies investigating the gut-liver axis are reviewed to identify therapeutic avenues for the prevention and treatment of liver dysfunction and ischemia-reperfusion injury. In-so-doing, novel pathways and perspectives can be exploited to develop therapies for the control of inflammatory hepatic ischemia-reperfusion injury, particularly following liver transplantation or surgical intervention.

Keywords: liver transplantation; liver injury; ischemia-reperfusion injury; gut microbiota; metabolic derivatives

Introduction

Each year, close to 800,000 individuals require liver transplantation (LTx) due to diseases induced by viruses, drugs, tumors, and related factors [1]. However, LTx carries the risk of ischemia-reperfusion injury (IRI), characterized by tissue damage resulting from the interruption and subsequent restoration of blood supply to an organ [2]. IRI also occurs in complex hepatectomies, hemorrhagic shock, and severe liver trauma surgeries. Despite advancements in surgical techniques and significant improvements with increased surgical experience, hepatic ischemia-reperfusion injury (HIRI) still results in numerous postoperative deaths due to severe complications. Despite numerous clinical interventions proposed for post-LTx or surgical IRI, including the free radical scavengers, modulation of cytokine response, and inhibition of immune system activation, these approaches have not yielded satisfactory outcomes in clinical practice. However, hypothermic *ex vivo* perfusion has been confirmed to mitigate liver damage [3]. Evidence from clinical and experimental studies has highlighted the significance of gut microbiota and their metabolic byproducts on hepatic pathologies [4,5]. However, investigations into the nexus among gut microbiota, its metabolic derivatives, and LTx or post-operative IRI are still at the foundational stages. The elucidation of the gut-liver axis offers a novel vantage point for the therapeutic intervention of HIRI. The concept of the gut-liver axis provides a new approach to therapeutically manage HIRI. It highlights the two-way communication between the gastrointestinal tract and the liver, primarily mediated by the portal venous system, which significantly influences the develop-

ment of hepatic disorders [6]. Increased intestinal permeability and bacterial translocation allow the passage of microbial metabolites to the liver, leading to the obstruction of bile acids (BAs) metabolism, gastrointestinal dysmotility, and systemic inflammation. These conditions can precipitate dysbiosis of the gut microbiota, thereby exacerbating hepatic injury [7]. Gut microbes, maintain the intestinal barrier integrity, modulate the immune system, and regulate metabolic activities and thus influence the occurrence of liver diseases [8]. For instance, they have been shown to affect outcomes of LTx by regulating inflammation. Reports indicate that in individuals post-LTx, the microbiome modulates the severity of liver disease and the occurrence of acute cellular rejection (ACR) [9]. Thus, understanding the immune pathways associated with microbial translocation and transplant rejection is essential for improving the prognosis of post-LTx patients. Although existing literature is limited, there appears to be a connection between the immune pathways activated by microbial translocation and liver organ rejection. One contributing factor is the disruption of the balance between regulatory T cells (Tregs) and effector T cells by the microbiome, leading to an increase in effector T cells and a decrease in Tregs [10]. Importantly, studies have revealed that metabolites produced by gut microbes, such as short-chain fatty acids (SCFAs), BAs, lipopolysaccharides (LPS), amino acids, and peptides, among others, influence the progression of liver diseases [8]. Although researchers have explored the potential of gut microbiota and its metabolic derivatives to treat liver diseases, there are several gaps and questions regarding their therapeutic efficacy. In summary, a deeper exploration of the complex interactions between the gut microbiota and its metabolites and liver diseases, particularly HIRI, is needed to unravel new strategies for alleviating HIRI and improving patient outcomes.

Overview of Hepatic Ischemia-Reperfusion Injury

HIRI is defined as an inflammatory and damage response caused by liver reperfusion after a period of ischemia. In the ischemic phase of IRI, anaerobic metabolism is enhanced due to reduced reductive substances, and upon reoxygenation, there is an excessive generation of oxygen free radicals as oxygen-requiring reducing substances are reintroduced [11]. These free radicals not only damage cells but also trigger inflammatory responses. During HIRI, these oxygen free radicals promote the production of High Mobility Group Box 1 (HMGB1) and activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [12], leading to the generation of various cytokines, including interleukins 1α and β (IL-1α and β), IL-2, IL-3, IL-6, IL-8, and tumor necrosis factors α and β (TNF-α and β). In this process, damaged hepatocytes produce and release reactive oxygen species (ROS), HMGB1, and damage-associated molecular patterns (DAMPs), all of which enhance neutrophil aggregation and activation of Kupffer cells (KCs) [13]. These cytokine cascades induce inflammatory responses and oxidative stress, and thus contribute to the development of inflammatory damage. This scenario is common in clinical procedures such as liver surgery, organ transplantation, and traumatic liver injury. Therefore, understanding the clinical background and pathogenesis of HIRI and developing more effective treatment and prevention strategies deserve significant attention. In LTx and surgeries, rapid restoration of blood supply to ischemic liver is crucial for avoiding or minimizing IRI. The process of IRI can be categorized into three stages: perfusion, ischemia, and reperfusion [14]. To mitigate damage during the reperfusion phase, several strategies have been devised, including ischemic preconditioning, postconditioning, and machine perfusion. Ischemic preconditioning (IPC), a brief period of ischemia, is recognized as an effective self-protective mechanism during the perfusion phase, enabling the liver to adapt to subsequent prolonged ischemia. However, the precise mechanisms behind this phenomenon are not understood [15]. Research by De Almeida and colleagues [16] found that liver preconditioning reduced lipid peroxidation and mitigated HIRI. Additionally, hypothermic preconditioning, remote ischemic preconditioning (RIPC), and statin preconditioning are considered to be effective strategies for alleviating IRI [17,18]. Although IPC can protect organs from IRI-induced damage, the duration determines the outcomes. Furthermore, because this approach is often applied preoperatively, its utility is predominantly confined to managing acute liver injury. However, determining the optimal duration and frequency of IPC cycles poses a challenge, which somewhat limits its broad clinical application [15]. During the ischemic phase, low temperatures should be maintained to minimize metabolic activity and alleviate organ dysfunction. Thus, techniques such as hypothermic machine perfusion (HMP), hypothermic oxygenated perfusion (HOPE), and normothermic machine perfusion (NMP) have been employed to preserve the physiological status and functionality of organs [19] (Fig. 1). During the reperfusion phase, ischemic postconditioning can ameliorate IRI [20]. The use of postconditioning alone or in combination with statins can potentially improve reperfusion injury [17,21]. Although they can alleviate HIRI, some of these strategies are costly and have practical application challenges in clinical surgical settings [22]. Moreover, studies have reported a close association between HIRI and gut microbiota [23]. However, evidence from such investigations into the effects of gut microbiota and its metabolic byproducts on HIRI is inconclusive. Examining the advancements and therapeutic approaches in investigating the gut-liver axis, specifically focusing on the involvement of gut microbiota and their metabolic byproducts in liver disease-related IRI, could yield valuable insights for shaping clinical trials and

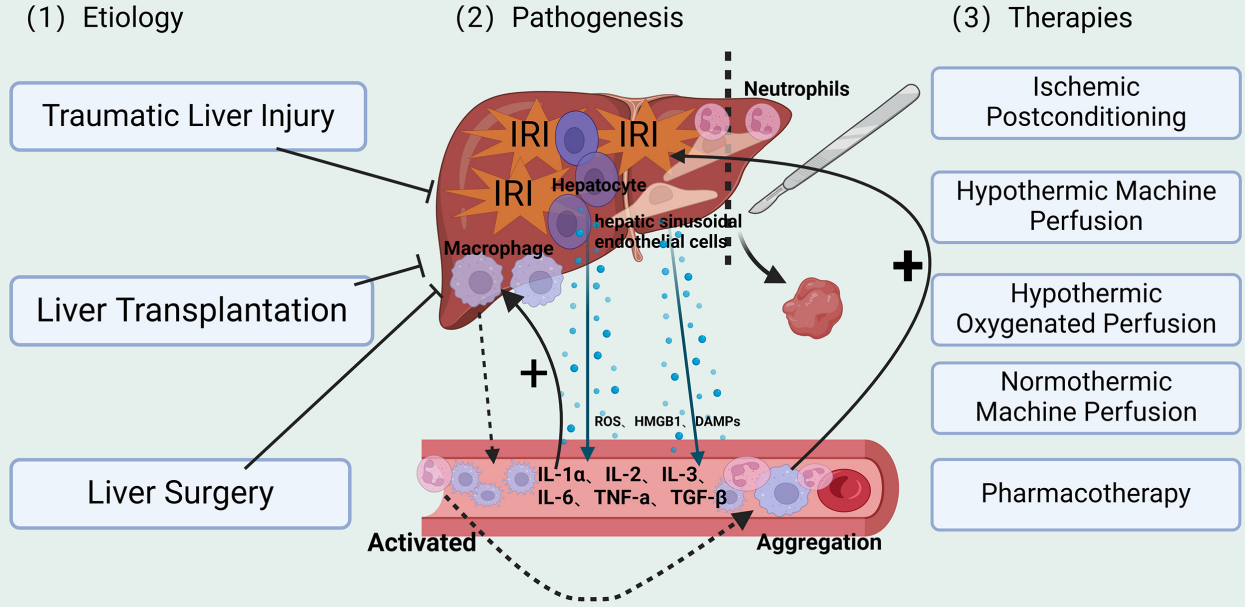

Fig. 1. The pathogenesis and progression of hepatic ischemia-reperfusion injury and current therapeutic approaches. (1) The etiology of IRI include traumatic liver injury, liver transplantation and liver surgery. (2) The pathogenesis of IRI involves inflammatory responses triggered by damage to hepatocytes and sinusoidal endothelial cells, among others. This damage promotes the production of HMGB, ROS, and DAMPs, leading to the generation of various cytokines, including IL-1α and β, IL-2, IL-3, IL-6, and TNF-α and β. These molecules enhance the aggregation of neutrophils and activation of Kupffer cells (KCs). The ensuing cytokine cascade induces further inflammatory reactions and oxidative stress, thereby facilitating the progression of inflammatory damage associated with IRI. (3) Current therapeutic strategies for IRI include ischemic postconditioning, hypothermic machine perfusion, hypothermic oxygenated perfusion, normothermic machine perfusion, and pharmacological treatments. IRI, ischemia-reperfusion injury; IL-1α, interleukin 1α; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor β; ROS, reactive oxygen species; HMGB1, High Mobility Group Box 1; DAMPs, damage-associated molecular patterns. (Created with BioRender.com).

research methodologies. Such insights have the potential to enhance patient outcomes, particularly for those undergoing liver transplantation or surgical procedures prone to postoperative IRI.

Overview of Gut Microbiota and Metabolic Products

The human gut microbiota refers to the collection of microorganisms residing in the digestive tract, including bacteria, archaea, viruses, fungi, and protozoa, with bacteria being the predominant group [24–28]. These microbial populations interact among themselves and with the host via direct contact, protein secretion, or the release of metabolic products. Through such interactions, they create a dynamic micro-ecosystem that influences human health and disease development [29–32]. Studies suggest that the gut microbiota participate in the initiation and development of diverse ailments, such as diabetes, hypertension, cardiovascular diseases, and cancers, and have been referred to as the "forgotten organ" of the human body [33–37]. Furthermore, the gene tally of the gut microbiota is projected to be approximately 100 times greater than that of the human genome, which has led to its designation as the "second genome" of the human body [38–40]. The gut microbiome predominantly consists of several phyla, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Clostridia, and Verrucomicrobia. Firmicutes and Bacteroidetes collectively constitute over 90% of the gut microbiota [41]. Within the Bacteroidetes phylum, the genus Bacteroides is prevalent and often associated with various pathological conditions [42]. In contrast, the Firmicutes phylum comprises a diverse range of genera, encompassing both Gram-positive and Gram-negative bacteria [41]. Gut microbiota, integrate different bodily components into a cohesive system via mechanisms such as the gut-liver and gut-brain axes, establishing a nuanced symbiotic relationship with the host. Interestingly, it accurately responds to alterations in both the internal and external milieu. Elements such as dietary habits, bacterial infections, environmental exposures, pharmacotherapy, and hepatic conditions including acute liver injury, chronic alcoholic liver disease, ischemia-hypoxia, hepatocellular carcinoma (HCC), and cirrhosis, can be driven by the gut microbiota dynamics [43–45]. Therefore, theoretically, HIRI is associated with gut microbiota and its metabolic products. Therefore, it is crucial to explore changes in gut microbiota and its metabolic products in response to HIRI, as well as their role in liver is-

chemia/reperfusion (I/R) injury. It has been demonstrated that the gut microbiota and its metabolic derivatives participate in various processes including nutrient assimilation, growth and development, the establishment of biological barriers, modulation of the immune system, lipid metabolism, and the execution of anti-neoplastic activities [46–48]. Notably, various dietary nutrients alter the human gut microbiota leading to the production of bioactive compounds such as BAs, SCFAs, LPS, ammonia, and phenols [49–52]. These metabolites produced by microbes act as crucial mediators for the communication between the microbiota and the host. Thus, dysregulation of these microbial communities and their metabolic byproducts can cause injury to the host and precipitate metabolic, immunological, and neurological disorders, such as diabetes, hypertension and atherosclerosis, inflammatory bowel disease, and autism [42,53–55]. Consequently, the gut microbiota and its metabolic outputs affect both the health of the host and disease pathogenesis. The gut-liver axis modulates the intricate interactions between microbial communities, engaging in numerous biochemical pathways some of which are not known. Mediated primarily through the portal vein, this bidirectional communication allows for direct transport of gut-derived substances to the liver. Conversely, liver influences the gut environment by secreting bile and antibodies [55]. Thus, the role of gut microbiota and its dysbiosis in liver diseases has attracted significant attention [56–59].

Dynamics of Gut Microbiota after Liver Transplantation or Surgery

The gut microbiota forms an ecosystem with more than 35,000 bacterial species [60]. These species have diverse functions such as protecting the intestinal barrier, modulating the immune response, and regulating metabolic processes [60]. Bacterial colonization begins at birth, with the composition usually normalizing within 2–3 years under the influence of environmental, genetic, and nutritional factors [61]. Alterations in the gut microbiota can affect outcomes of LTx. Research indicates that in rats subjected to LTx, the populations of beneficial bacteria, including Bifidobacteria and Lactobacilli, are significantly decreased, while the numbers of pathogenic bacteria such as *Enterobacteriaceae* and Enterococci is significantly increased [62] (Fig. 2).

Wu *et al*. [63] further demonstrated that, besides Enterococci, the number of specific bacterial strains normalized over time post-LTx. This modification may result from the transplantation process transferring donor microbiota to the recipient [63]. Moreover, Bajaj *et al*. [7] found that following LTx, there is a shift in the functional profile of the gut microbiota. Specifically, the relative abundance of *Enterobacteriaceae* post-LTx is decreased, while that of Veillonellaceae and Helicobacteriaceae is increased. These changes are associated with the improvement of LPS synthesis, regulation of ammonia and BAs, and methanogenesis, highlighting the significant impact of the liver on gut microbial functions. The composition of gut microbiota is dynamic in patients pre- and post-LTx, with improvements in liver function post-LTx being closely associated with these microbial changes. The interplay between gut microbiota and liver regeneration has been investigated in several animal models undergoing partial hepatectomy [7]. Findings from such studies show that there are dynamic shifts in the composition of gut microbiota from 0 hours to 9 days following the procedure [64]. For instance, after partial hepatectomy, significant alterations in the gut microbiota composition were observed, characterized by an initial surge in Bacteroidetes and a reduction in Firmicutes as early as 1-hour post-operation. At the taxonomic family level, a notable increase in the Bacteroidetes families, specifically S24-7 and Rikenellaceae, was observed, whereas in the Firmicutes phylum, there was a decline in Clostridiaceae, Lachnospiraceae, and Ruminococcaceae. The modifications in these microbial communities, including S24-7, Lachnospiraceae, and Ruminococcaceae, exhibit a close relationship with the liver's metabolic functions and regenerative capacity. In mice subjected to partial hepatectomy, alterations in bacterial populations persisted for 9 days, spanning the initiation, proliferation, and termination phases of liver regeneration [64]. Similarly, in rats, variable changes in gut microbiota composition were observed following partial hepatectomy [65]. In the mentioned research, a rapid diminution in the abundance of Bacteroidetes was observed within the initial 12 hours following the surgical procedure, which then reverted to baseline figures at the 48-hour mark, decreased once more at 72 hours, and persisted at a reduced level until the conclusion of the study. In contrast, Firmicutes displayed a unique trend relative to Bacteroidetes throughout liver regeneration, as indicated by variations in the Firmicutes/Bacteroidetes ratio (F/B ratio) over the observation period. Moreover, there was a significant increase in abundance of Proteobacteria levels 48 hours post-partial hepatectomy, followed by a gradual return to baseline levels by the study's conclusion. Within the first 12–24 hours and from the third to the fourteenth day following surgery, there was a noticeable rise in the populations of Lachnospiraceae and Ruminococcaceae, which subsequently diminished during the 30–48-hour interval. Cluster analysis revealed fluctuations in the composition of the gut microbiota during liver regeneration [65]. The abundance of certain bacterial species fluctuated over the postoperative period rather than remaining consistent. Consequently, adjusting the diversity of gut microbiota could represent a potential approach for managing LTx or surgical IRI. However, this hypothesis needs to be validated through animal experiments or clinical trials. This is also a key research area that our team plans to explore further in the future.

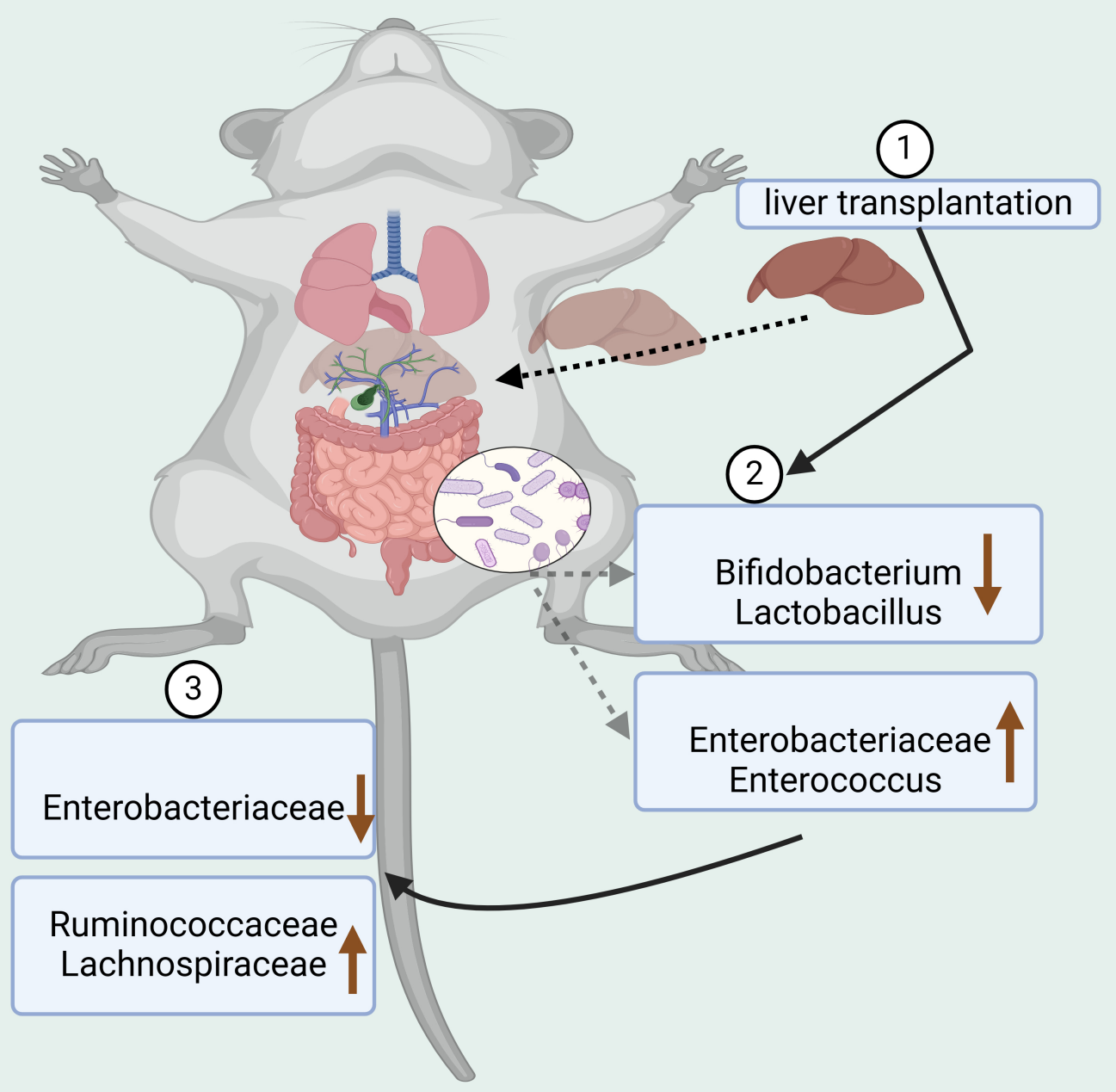

Fig. 2. The dynamics of gut microbiota after liver transplantation or surgery. ① Mouse liver transplantation (LT). ② After LT in rats, the number of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* significantly decreases, while the number of harmful bacteria like *Enterobacteriaceae* and *Enterococcus* significantly increases. ③ After LT, the functionality of gut microbiota also changes, with a significant decrease in the relative abundance of *Enterobacteriaceae*, and an increase in the relative abundance of *Ruminococcaceae* and *Lachnospiraceae*. (Created with BioRender.com).

Relationship Between Gut Microbiota and HIRI

HIRI is closely linked to the gut microbiota. Tregs play a crucial role in mitigating IRI-induced ACR response by modulating immune responses, thus enhancing the tolerance of allogeneic liver transplants [66,67]. It is noteworthy that fragile Bacteroidetes and their capsular polysaccharides in the gut can facilitate the differentiation of CD4 T cells into Tregs post-LTx dysregulation. This process aids in preventing the worsening of inflammation and suppressing excessive immune responses, highlighting the critical role of gut microbiota in modulating immune responses post-transplantation. This interaction underscores the potential therapeutic strategies targeting gut microbiota to enhance transplant outcomes and reduce the risk of post-transplant complications [68] (Fig. 3).

As critical contributors to autoimmune conditions, T helper 17 (Th17) cells produce cytokines such as IL-17, IL-22, and IL-26. These cytokines can initiate potent inflam-

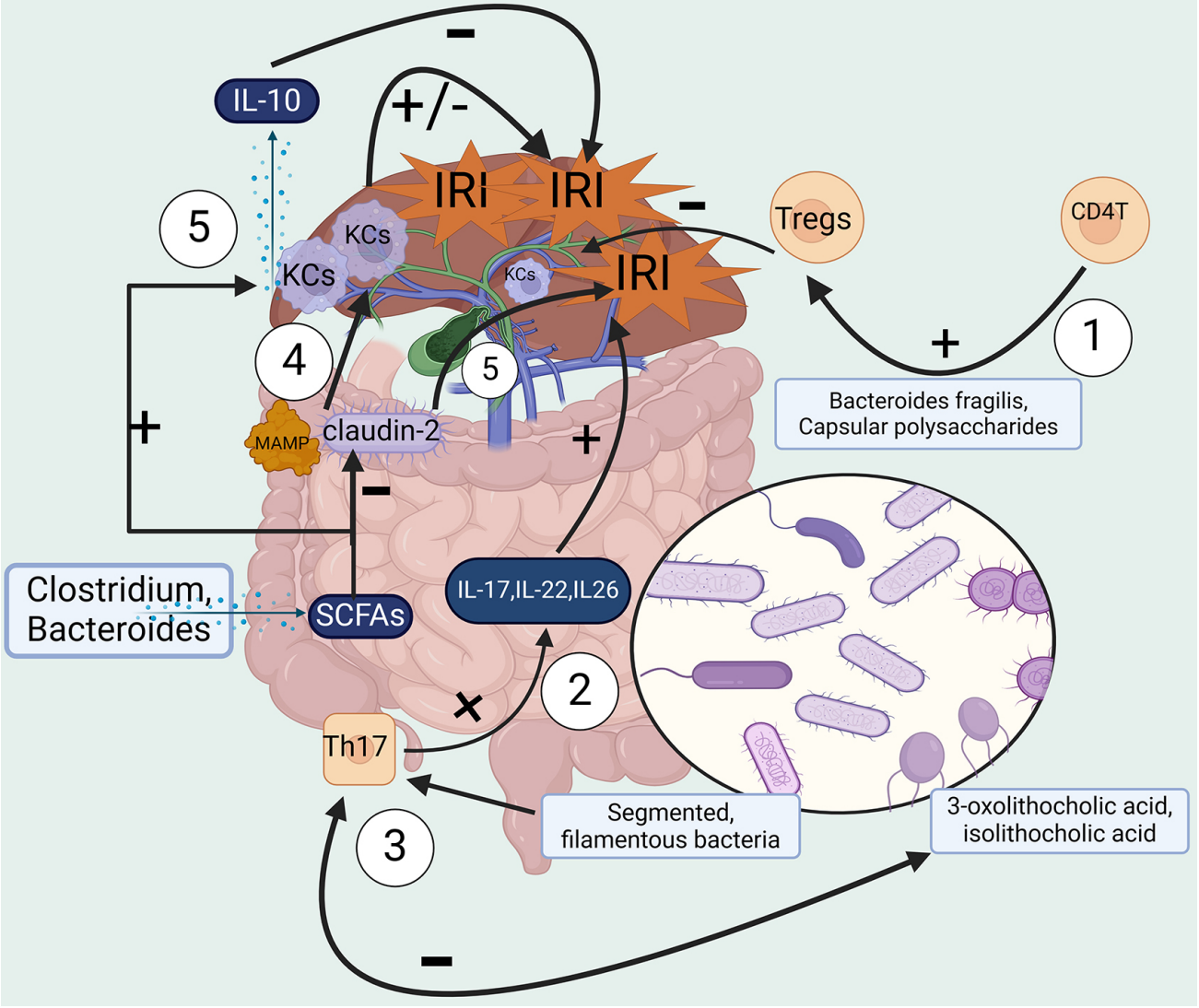

Fig. 3. Relationship between gut microbiota and hepatic ischemia-reperfusion injury. ①: Fragilis Bacteroides and capsular polysaccharides in the gut can induce the differentiation of CD4 T cells into Tregs following liver transplant dysbiosis, thereby alleviating ischemia-reperfusion injury post liver transplantation. ②: Th17 cells secrete IL-17, IL-22, and IL-26 during ischemia/reperfusion (I/R), potentially triggering a strong inflammatory response and exacerbating I/R injury. ③: Segmented filamentous bacteria in the gastrointestinal tract can induce the differentiation of Th17 cells, thereby defending against intestinal pathogen invasion. 3-oxo bile acids and isoallocholic acid are capable of regulating the Th17/IL-17 signaling axis, with a negative correlation existing between them. ④: The number of Kupffer cells (KCs) is determined by gut bacteria and constitutive microbial-associated molecular patterns (MAMPs). ⑤: Clostridium butyricum and Bacteroides can produce short-chain fatty acids (SCFAs), inducing the expression of IL-10 and downregulating the expression of claudin-2 in the small intestine, thereby preventing I/R injury in intestinal TLR9-deficient mice. KCs, Kupffer cells; Tregs, regulatory T cells; SCFAs, short-chain fatty acids; MAMP, microbe-associated molecular pattern. (Created with BioRender.com).

matory reactions and worsen I/R damage [69]. Research demonstrates that segmented filamentous bacteria residing in the mouse intestinal tract specifically promote the differentiation of Th17 cells, which enhances the defense against pathogens in the gut [70]. BAs, including 3-oxo-lithocholic acid and isoallolithocholic acid, have been found to regulate the Th17/IL-17 signaling pathway, exhibiting an inverse relationship between their levels and activity [71]. Corbitt *et al*. [72] found that the population of Kupffer cells (KCs) was influenced by intestinal microbiota and an array of microbe-associated molecular patterns (MAMPs) delivered via the portal vein bloodstream. Eliminating gut bacteria may result in a shortage of KCs, subsequently affecting liver IRI. Deactivating KCs can mitigate IRI, and the gut microbiome plays a crucial role in shaping the response of KCs to IRI [73]. Moreover, Nakamura *et al*. [74] revealed that mice with modified intestinal microbiota, as a result of antibiotic treatment, exhibited decreased levels of sinus

congestion, edema/vacuolization, and hepatocyte necrosis following allogeneic liver transplantation. This suggests a diminution in IRI [74]. Clostridia and Bacteroidetes—known for their ability to generate SCFAs—trigger IL-10 upregulation and suppress claudin-2 expression in the small intestine. This process helps in averting IRI, intestinal apoptosis, and inflammation in mice lacking Toll-like receptor 9 (TLR9) [75,76].

In summary, the extent of IRI is closely associated with the restoration and preservation of organ function following LTx. The intestinal microbiome, acting as a pivotal regulator in IRI, presents a promising therapeutic strategy to enhance the outcomes of liver transplantation.

Microbial Metabolites and HIRI

SCFAs

SCFAs, also known as volatile fatty acids, are primarily produced by anaerobic bacteria in the colon through the fermentation of undigested carbohydrates such as oligosaccharides, non-starch polysaccharides, and resistant starch. The most abundant SCFAs include acetate, propionate, and butyrate. They play a vital role in sustaining normal colonic functions and the structure and operation of colonic epithelial cells in human metabolism [77]. SCFAs modulate intestinal and overall host metabolism through the activation of G protein-coupled cell surface receptors, specifically G protein-coupled receptors 41 (GPR41) and GPR43 [78]. The receptors for SCFAs are not only located in the intestines but also in adipose, muscle, and liver tissues throughout the human body. This suggests that SCFAs can directly influence the metabolism of substrates and energy in peripheral tissues. Research has indicated that SCFAs such as propionate and butyrate play a pivotal role in mitigating hepatic HIRI in mice [79]. Butyrate — an SCFA and histone deacetylase (HDAC) inhibitor—can reduce the production of pro-inflammatory cytokines *in vivo* and *in vitro* [80,81]. It has been reported that butyrate reduces the production of myeloperoxidase (MPO), an enzyme in neutrophils and a broad marker of neutrophil infiltration, in the liver and several inflammatory factors in serum [82]. By generating oxidative stress, neutrophils activate KCs and lead to microvascular dysfunction and edema [83]. Previous reports indicate that HIRI can increase MPO activity in the liver [84]. Pre-treatment with butyrate in the liver significantly reduces MPO activity, suggesting that butyrate-induced reduction of MPO activity might be due to its role in mitigating inflammation-induced liver damage by inhibiting oxidative stress. Notably, the content of malondialdehyde (MDA) in liver tissue increases sharply during I/R; however, MDA content is significantly reduced by butyrate [79]. Therefore, the mechanism by which butyrate alleviates HIRI might be related to its antioxidant activity. TNF-α and IL-6, as important pro-inflammatory cytokines, contribute to the recruitment of neutrophils in the liver. Butyrate also inhibits the increase in *TNF-α* and *IL-6* mRNA levels in mice while enhancing the production of the anti-inflammatory cytokine IL-10 [85]. Whether butyrate can increase IL-10 expression in the liver after I/R remains inconclusive and warrants further elucidation. Besides, although the hepatoprotective effect of butyrate may be attributed to its inhibitory effect on inflammatory factors, its specific related signaling pathways are yet to be elucidated, necessitating further research. Given its low-risk factors, butyrate may be a promising therapeutic strategy for liver IRI in clinical liver surgery. Therefore, its potential therapeutic value should be further validated in large animal models and clinical trials. A separate investigation on rats revealed that a high-inulin diet significantly boosted propionate levels, underscoring its antioxidant capability in enhancing recovery from IR-induced liver damage. This improvement was achieved through the modulation of gut microbiota and an elevation in propionate levels in the portal vein [86]. In this study, propionate was proven to directly inhibit the activation of TLR4 triggered by HMGB1 in macrophages, reducing the production of TNF-α, thereby mitigating the inflammatory response. This protective effect is primarily achieved by increasing the anti-oxidative and anti-apoptotic actions of propionate in hepatocytes in the portal vein, thereby activating the acetylated histone-3/Forkhead Box O1/Heme Oxygenase 1 (FOXO-1/HO-1) pathway, which leads to the suppression of cell death and reduced the release of HMGB1 from necrotic cells, thus alleviating liver IRI [86]. Propionate and butyrate also play a role in the generation and function of Tregs by inhibiting histone deacetylases [87,88]. These studies underscore the dynamic interplay between SCFAs derived from gut microbiota and the host's immune and metabolic equilibrium. This relationship may be critical in formulating efficacious therapeutic strategies in clinical environments. While various studies indicate that SCFAs can exhibit pro-inflammatory effects and activate the immune system [89,90], this phenomenon is inapplicable in the context of LTx. Prior clinical research in the context of LTx has demonstrated that SCFAs can diminish HIRI without negatively impacting the immune system [84,91], consistent with other reports of SCFAs with anti-inflammatory and immunosuppressive functions [84,91–93]. Hence, it has been established that SCFAs enhance macrophage activation and mediate systemic adaptive immune responses by suppressing cytokine production and T cell activation while promoting the activation of Tregs [80,91]. In addition to problems stemming from alterations in the microbiome itself, dysbiosis may also alter the production of SCFAs, impacting the immune system by heightening its activity. The increase in immune activity may elevate the risk of inflammation and graft rejection [63]. Thus, how to modulate microbial metabolites to alleviate graft rejection-induced liver IRI remains a significant challenge.

Lipopolysaccharides (LPS)

LPS, large biomolecular compounds typically localized on the outer membranes of gram-negative bacteria, protect cells and regulate their functions. LPS comprise the lipid component in the cell membrane and the polysaccharide component on the outer side. Gut-derived LPS have significant physiological functions, including activating immune responses in the immune system. Within the framework of the gut-liver axis, preconditioning with low doses of LPS is believed to provide resilience against LPS-induced inflammatory damage or tissue damage triggered by stimuli other than LPS. This phenomenon has been extensively documented across various organs, such as the brain, heart, pancreas, kidneys, retina, and liver [94–97]. LPS preconditioning upregulates specific negative regulators of the TLR1 signaling pathway, such as cytokine signaling inhibitor 3 (SOCS-3), SOCS-4, and interleukin-1 receptor-associated kinase M (IRAK-M), and inhibits inflammation after liver I/R by suppressing NF-κB and c-Jun N-terminal kinase (JNK) [98]. Additionally, TLR activation has been reported to inhibit the activation transcription factor 4-CCAAT/enhancer-binding protein homologous protein (ATF4-CHOP) pathway of the unfolded protein response, thus promoting apoptosis and inflammation in various pathological processes [99]. Apoptosis and necrosis are key processes of cell death in the context of HIRI, directly reflecting the extent of cell death. Prolonged and excessive endoplasmic reticulum (ER) stress leads to apoptosis. Previous studies have shown that ER stress is involved in IR in various organs, including the heart, kidneys, lungs, brain, and liver [100–102]. The stress response of the ER is initiated through the activation of three distinct signaling pathways, which are mediated by protein kinase RNA-like endoplasmic reticulum kinase (PERK), inositol requiring enzyme-1 (IRE-1), and activating transcription factor 6 (ATF6). Although the mechanisms by which ER stress leads to apoptosis have been only partially elucidated, certain specific elements have been recognized, including C/EBP homologous protein (CHOP, also referred to as the growth arrest and DNA damage-inducible gene), which was initially identified in the context of DNA damage [103]. CHOP is primarily activated by the ATF4 pathway [99,104,105]. Another research finding highlighted for the first time the importance of inhibiting the ATF4-CHOP pathway, which is critical for the protective preconditioning conferred by low-dose LPS against liver IRI. This inhibition not only prevents hepatocyte apoptosis by inhibiting the activation of Cysteine-aspartic acid protease 12 (caspase-12) and caspase-3 but also reduces inflammatory responses by suppressing NF-κB and mitogen-activated protein kinase (MAPK) inflammatory signaling pathways [106]. This discovery unveils a novel molecular mechanism through which LPS preconditioning safeguards against hepatocyte damage caused by liver IRI. Consequently, targeting the ATF4-CHOP pathway could represent an innovative therapeutic approach to alleviate IRI in liver surgeries. Contrary to the above findings, LPS can induce sepsis, wherein the liver plays a central role in the phagocytosis and clearance of toxins, and continuous stimulation by LPS leads to liver damage [107,108], thereby exacerbating HIRI. Whether the inflammatory signaling pathways involved in LPS-induced HIRI exacerbation are consistent with those mitigated by low-dose LPS needs further validation. It has been reported that gut-derived LPS activates KCs to release pro-inflammatory mediators (such as TNF-α, IL-1, and IL-10), lysosomal enzymes (including proteases and phosphatases), and superoxides, all of which collectively exacerbate the inflammatory response and necrosis in HIRI [109]. Previous studies using animals with TLR4 deficiency, gut sterilization, and LPS treatment demonstrated that gut-derived LPS contributes to the development of hepatocellular carcinoma (HCC) [110,111]. Although the significant influence of gut-derived LPS on liver injury is widely recognized and accepted, translating this understanding into effective treatments presents considerable challenges and necessitates additional investigation. Moreover, compromised liver regeneration has been documented in germ-free mice subjected to partial hepatectomy and rats subjected to both partial hepatectomy and colonic resection [112,113]. Therefore, gut-derived LPS plays a critical role not only in liver injury, fibrosis, and IRI but also in liver regeneration. The impact of LPS likely varies depending on the extent and duration of exposure. Nonetheless, pinpointing the beneficial levels of gut-derived LPS for the liver across various scenarios remains an intricate task. This careful balance is essential to circumvent the detrimental consequences of excessively activating TLR4. A viable approach may involve managing the gut microbiota using probiotics, prebiotics, and selective antibiotics (such as rifaximin), to modulate levels of gut-derived LPS. However, most anti-LPS drugs (such as antibiotics and antibodies) show little clinical activity against liver injury, e.g., polymyxin antibiotics and polymyxin B (PMB), which have been utilized to neutralize LPS since the 1950s but are limited to short-term use due to their toxicity [114,115]. The widespread use of antibiotics leading to resistant bacteria and LPS release further complicates the issue [116]. Therefore, developing novel drugs and strategies targeting LPS to mitigate the cascade of inflammatory responses caused by liver IRI is urgent.

BAs

BAs are compounds produced by the host and modified by intestinal bacteria, which the host recognizes and regulates to maintain various aspects of health. Primary BAs, including cholic acid and chenodeoxycholic acid, are produced in the liver through cholesterol oxidation and conjugated with taurine or glycine to form bile salts [117]. Bile salts are secreted into the biliary tree and ducts, with branches of bile-containing ducts eventually delivering bile

to the upper gastrointestinal tract. Conjugated bile salts reaching the ileum can be reabsorbed by the host and transported back to the liver to maintain the BA pool. However, upon entry into the intestine, BAs are metabolized by bacteria into secondary BAs, i.e., deconjugated primary BAs, depending on the bacteria's expression of bile salt hydrolase [118]. Secondary BAs can produce deoxycholic and lithocholic acids through dehydroxylation [119]. Manipulation of BAs can produce agonists and antagonists of these receptors, complicating the beneficial or detrimental effects of BAs and their metabolic end-products on health and diseases. Several nuclear- and membrane-bound receptors that bind to BAs have been reported and classified based on their specific recognition of bile in other microbial products [120]. The receptors that directly recognize multiple BAs include the farnesoid X receptor (FXR) expressed in most intestinal cells and G protein-coupled receptor 5 (TGR5) located in specialized cells called L cells. Experiments involving liver injury in rodent models suggest that stimulating FXR-mediated signaling can improve steatohepatitis, portal hypertension, and liver inflammation [121]. Another animal experiment confirmed that depletion of gut microbiota changed the composition of liver BAs, leading to FXR activation, which can directly regulate TLR4 transcriptional activity, reducing cell apoptosis and inflammatory responses to further alleviate liver IRI [122]. Overall, FXR agonists are promising anti-inflammatory drugs for the liver. Therefore, transcriptional signaling mediated by BAs as nuclear receptor ligands, such as FXR, can significantly impact liver IRI. Regarding the regulation of inflammation in liver diseases, BAs can influence the differentiation and function of T cells. This includes modulating both pro-inflammatory TH17 cells and anti-inflammatory Tregs [123], suggesting that BAs can both exacerbate and alleviate inflammation in liver IRI; however, the related signaling pathways warrant further elucidation. Conde de la Rosa *et al*. [124] found that total BA levels in the liver were significantly increased in patients with HCC, highlighting the pivotal role of BA accumulation in the development of HCC due to its contribution to cell damage. Hence, modifying the type or amount of BAs in patients with HCC could diminish inflammation. This adjustment may aid in devising effective strategies for managing post-transplant IRI in end-stage liver cancer. Additionally, in terms of liver metabolic regulation, Ma *et al*. [125] discovered that BA synthesis mediates the upregulation of C-X-C motif ligand 16 (CXCL16) in mice, which controls the accumulation of wild-type natural killer T (NKT) cells. This process also regulates the expression of CXCL16 in human liver sinusoidal endothelial cells (LSECs) [125], thereby affecting the expression balance of LSECs. LSECs line the blood vessels of the liver, controlling vascular tension and thus the flow of nutrients and oxygen to hepatocytes. The expression of cell adhesion molecules in LSECs is upregulated after liver injury, playing a key role in the accumulation, activation, and regulation of cells in response to liver IRI. Normal LSEC function is vital in protecting the liver from disruption of homeostasis following IRI [126]. Thus, developing drugs targeting the BA/CXCL16/NKT signaling pathway in liver IRI could be a new research strategy. Overall, the effects of other gut microbial metabolites on liver IRI, including choline metabolites, phenolic derivatives, and indole derivatives, warrant further investigation. Exploring these avenues will uncover additional regulatory mechanisms that connect liver IRI with microbial metabolites, paving the way for the development of therapies centered on gut microbiota and their metabolites.

Modulation of Gut Microbiota to Prevent Liver Disease-IRI

Antibiotic Preconditioning (ABP)

In rats subjected to LTx, it was found that administration of polymyxin B sulfate for 7 days decreased *Enterobacteriaceae* populations while enhancing the abundance of Bifidobacteria, Lactobacilli, Bacteroides, and Actinobacteria. This shift in gut microbiota composition was driven by the decrease in endotoxemia and the production of TNF-α [127]. A comparable outcome was obtained in a small-scale retrospective study investigating the effects of rifaximin, an antibiotic. This study highlighted the benefits of rifaximin in reducing inflammatory damage after LTx in patients with end-stage liver disease [128]. Two retrospective analyses also support these findings, suggesting that prophylactic antibiotic use, including rifaximin, neomycin, erythromycin, and ampicillin-sulbactam, prior to long-term treatment initiation, may decrease infection rates. Such preventive measures can prevent liver damage, alleviate inflammation, and decrease early allograft dysfunction post-transplantation [74,129,130]. To date, only one single randomized clinical trial has evaluated the effect of gut decontamination on changes in gut microbiota after LTx based on fecal cultures. They found that Gram-negative bacteria was decreased in the decontamination group compared to the control group, although the rates of infection following LTx were not significantly different between the two groups [131]. Based on these findings, the role of gut decontamination in the post-operative setting needs to be further clarified [132]. Currently, few studies have investigated alterations in gut microbial populations and diversity resulting from liver I/R and how these changes affect liver function and regeneration. Moreover, the impact of antibiotic-induced modulation on gut microbiota and liver function remains to be clarified. Notably, the available investigations did not focus on evaluating the effect of antibiotic treatment on shifts in gut microbiota within fatty or aging livers subjected to surgery. Although the application of antibiotics decreased liver damage induced by ACR in rats

Table 1. Current experimental research is concentrated on the modulation of gut microbiota as a strategic approach to mitigate hepatic ischemia-reperfusion injury.

Researcher	Trial Name	Description	Trial type	Years
Ren J *et al*. [134]	Alteration in gut microbiota caused by time-restricted feeding alleviate hepatic ischaemia reperfusion injury in mice	Time-restricted feeding enhanced intestinal barrier function, leading to improved energy metabolism, reduced inflammation and oxidative stress, and decreased hepatocyte apoptosis and proliferation, collectively augmenting resistance to I/R injury.	Animal	2019
Kawasoe J *et al*. [86]	Propionic acid, induced in gut by an inulin diet, suppresses inflammation and ameliorates liver ischemia and reperfusion injury in mice	Inulin-rich diets enhance gut microbiome-mediated propionate production, which increases in the portal vein, exerting antioxidative and anti-apoptotic effects on hepatocytes. This activation of the acetylated histone-3/Forkhead Box O1/Heme Oxygenase 1 (FOXO-1/HO-1) pathway leads to reduced cell death and decreased HMGB-1 release from necrotic cells, ameliorating liver IRI in mice.	Animal	2022
Wang F *et al*. [135]	Gut microbiota-derived gamma-aminobutyric acid from metformin treatment reduces hepatic ischemia/reperfusion injury by inhibiting ferroptosis	Metformin mitigates liver IRI in mice by alleviating hepatic iron death induced by hepatic ischemia-reperfusion injury (HIRI), achieved through the remodeling of the gut microbiome.	Animal	2024
Nakamura K *et al*. [74]	Antibiotic pretreatment alleviates liver transplant damage in mice and humans	Antibiotic pretreatment mitigates liver IRI in mice and humans by altering the immune phenotype via gut microbiome composition changes. This is mediated through the interaction between PGE2-EP4 signaling and molecules related to endoplasmic reticulum (ER) stress and autophagy.	Clinical, Animal	2019
Nakanuma S *et al*. [136]	Pretreatment with a phosphodiesterase-3 inhibitor, milrinone, reduces hepatic ischemia-reperfusion injury, minimizing pericentral zone-based liver and small intestinal injury in rats	Administration of milrinone significantly improves mucosal damage, villous congestion, and apoptosis in the small intestine of mice, preventing hepatic injury caused by translocation of the gut microbiome to the liver, thereby ameliorating liver ischemia-reperfusion injury.	Animal	2020
Han SJ *et al*. [76]	Intestinal Toll-like receptor 9 (TLR9) deficiency exacerbates hepatic IR injury via altered intestinal inflammation and short-chain fatty acid synthesis	Exogenous administration of butyrate or propionate induces IL-10 expression and downregulates claudin-2 expression in the small intestine, attenuating intestinal cell apoptosis and inflammation. This consequently prevents liver ischemia-reperfusion (IR) injury and intestinal apoptosis/inflammation in mice with intestinal TLR9 deficiency.	Animal	2020
Cheng MX *et al*. [137]	VEGF-C attenuates ischemia reperfusion injury of liver graft in rats	Exogenous VEGF-C alleviates liver graft damage from IRI by modulating intestinal wall congestion and bacterial translocation. It attenuates macrophage inflammation via gut-associated TLR4 signaling, reducing the inflammatory response to Gram-negative bacterial infections and shifting Kupffer cell polarization from M1 to M2.	Animal	2019

undergoing LTx, it was observed that the gut barrier was compromised and disrupted, altering the microbiome's diversity [133]. This discovery carries significant clinical implications, suggesting that antibiotics can modulate gut microbiota. However, due to inconsistencies and discrepancies in current research, further randomized clinical trials and liver transplantation models are needed to expand our understanding of the impact of antibiotics. These investigations should aim to elucidate the exact mechanisms by which antibiotics affect liver function amidst alterations in the gut microbiome [129]. We acknowledge that although antibiotic therapy can mitigate infections and ameliorate hepatic I/R injury, there is a need to identify alternative approaches. Strategies targeting gut microbiota modulation present a promising avenue for enhancing the management of HIRI. Table 1 (Ref. [74,76,86,134–137]) illustrates some of the gut microbiota modulation trials reported.

As mentioned in previous sections, several factors such as liver injury, alterations in gut microbiota and changes in microbial metabolites have significant effects. Moreover, the side effects associated with antibiotic treatment should be considered. Antibiotics have been shown to induce multidrug-resistant bacteria. Recent research has suggested that colonization by multidrug-resistant organisms may be a pivotal indicator of dysbiosis in patients undergoing liver transplantation. This persistent imbalance in the gut microbiome may negatively affect the efficacy of therapies targeting hepatic I/R injury, underscoring the complex interplay between antibiotic use, microbial resistance, and transplant outcomes [138].

Probiotics and Prebiotics

Probiotics (beneficial microbial communities) can modulate the balance of gut microbiota. The use of probiotics not only enhances the beneficial microflora but also inhibits the growth of harmful bacteria. This approach highlights the significance of employing probiotic therapy to manage the dynamics of intestinal microbes, creating an environment conducive to optimal gastrointestinal well-being. Moreover, prebiotics, a class of oligosaccharides and cellulose metabolizable by gut microbiota, are a source of substrates needed to support bacterial growth. It has been demonstrated that prebiotics intake can increase beneficial bacteria, improve the composition and function of the gut microbiota and ameliorate hepatic steatosis [139], and thus can be used to alleviate I/R in patients post-LTx. For example, administration of *Lactobacillus paracasei* F19 showed the potential to mitigate the effects of ischemia/reperfusion on hepatic and gastrointestinal microbial populations in rodent models fed on either a normolipidemic or hyperlipidemic diet. These benefits were more pronounced in models lacking steatotic alterations [140]. Thus, the application of probiotics and prebiotics may be an effective therapeutic approach for improving the prognosis of patients with I/R injury. These theories are supported by evidence from both human clinical trials and animal studies. Recent findings suggest that probiotic supplementation can alleviate liver damage induced by pharmacological agents in animal models. Specifically, *Lactobacillus rhamnosus* was reported to promote hepatic function and reduce liver injury induced by alcohol consumption in murine models [141,142]. Pretreatment with *Bifidobacterium adolescentis*, *Bacillus coagulans*, and *Lactobacillus helveticus* can modulate the composition of gut microbiota and ameliorate hepatic damage in rat models administered with D-galactose (D-Gal) [143–145]. The beneficial effects of probiotics have been documented not only in animal experiments but also in some clinical trials [146–148]. A meta-analysis comprising four controlled trials with 246 participants found that liver transplant recipients administered with prebiotics and probiotics either prior to transplantation or on the day of surgery exhibited significantly lower rates of postoperative infections (7% versus 35%), shorter durations of hospital and intensive care unit stays, and decreased reliance on antibiotics [149]. Another placebo-controlled clinical trial involving 55 LTx recipients reported that probiotic treatment significantly decreased infection rates at 30 and 90 days post-transplant, with lower bilirubin levels and faster decline in transaminases [150]. Furthermore, probiotics has been found to prevent infections following LTx in hepatic injury IRI patients, without causing significant adverse effects [132]. In mice experiments, supplementation of Bifidobacteria and Lactobacilli ameliorated IRI by lowering plasma endotoxin concentrations and restoring intestinal barrier integrity [151]. Moreover, in a rat model of LTx, the abundance of these bacteria was increased following ischemic preconditioning, leading to amelioration of IRI [152], suggesting that probiotics may have similar benefits to IPC, a technique known to be protective against IRI [153,154]. This is ascribed to the potential of probiotics to produce SCFAs. As previously mentioned, SCFAs act as immunomodulators to alleviate inflammation by regulating KCs activation [84,91]. The benefits of probiotic supplementation in the context of liver surgery and post-surgical care such as attenuating inflammation and improving prognostic outcomes underscore the important interplay between hepatic function and gut microbiota. This interaction is facilitated by components and metabolites derived from the gut microbiome, all of which influence the process of hepatic regeneration. However, the mechanisms of interaction between probiotics and the liver are not fully elucidated. Therefore, the application of probiotics and prebiotics in the clinical setting for LTx or postoperative liver injury need to be further investigated.

Fecal Microbiota Transplantation (FMT)

FMT is the process of transferring beneficial intestinal microbes from a healthy donor's stool into a recipient, to therapeutically modify or restore the recipient's gut microbiota composition. Zhou *et al*. [155] demonstrated that

FMT not only increased butyrate levels and reduced endotoxin levels but also enhanced hepatic immunity in a mouse model of high-fat diet-induced non-alcoholic steatohepatitis (NASH). This study provides significant insights into the treatment of HIRI, although the interplay between FMT and gut microbiota metabolites such as SCFAs in reducing inflammatory injury is worthy of further exploration. Wang *et al*. [156] proposed that FMT could safeguard against damage to the intestinal mucosal barrier in mice models of hepatic encephalopathy and curtail systemic inflammatory reactions. Additionally, no infections attributed to the FMT procedure were reported in immunocompromised patients with Clostridium difficile infections who underwent FMT, underscoring its clinical efficacy and safety [157]. One significant concern associated with FMT is the risk of transmitting diseases due to the transfer of live microorganisms, whose composition is notably variable and unpredictable. Furthermore, the efficacy and outcomes of FMT can be influenced by external variables, including dietary habits and pharmaceutical interventions, further complicating its application and potential success. Therefore, more precise manipulation of the gut microbiota is needed. Moreover, further research should conduct to address these challenges and uncertainties before FMT can be used for treating liver IRI.

Use of Immunosuppressants

Immunosuppressants are a class of drugs that reduce inflammatory responses and immune-related injuries by suppressing the activity of the immune system. Recent studies have demonstrated that immunosuppressants can modulate the gut microbiota and alleviate HIRI. Although survival outcomes post-LTx have continuously improved with advancements in immunosuppressive therapy [158], insufficient or excessive immunosuppression is associated with an increased risk of ACR, higher incidence of infections, augmented drug toxicity, and increased mortality [159–163]. A previous study investigated the impact of immunosuppressants on the gut microbiota in rats following LTx and found that cyclosporine A improved liver injury post-LTx and partially restored the gut microbiota [164]. Optimal dosing of tacrolimus (FK506) induced normal transplant function in rats and stabilized the gut microbiota post-LTx. This led to an increase in beneficial bacteria, including Prevotella and *Bifidobacterium*, and a decrease in pathogenic endotoxin-producing bacteria, such as Bacteroides-Prevotella group and *Enterobacteriaceae*. Therefore, utilizing the gut microbiome could be a novel strategy for assessing immunosuppressive drug dosing and its impact on LTx recipients [165], which may allow the development of clinical treatment strategies to promote recovery from HIRI.

Targeted Molecular Therapy

Currently, the key signaling pathways modulating the pathogenesis of HIRI are poorly understood and deserve significant attention. For instance, targeting TLR signaling pathways can be achieved using TLR inhibitors, such as antibodies against TLR2 and TLR4 [122], to block the transmission of inflammatory responses. In terms of the gut-liver axis signaling pathway, the use of receptor agonists or inhibitors for gut microbiota metabolites can regulate the signaling between gut microbiota metabolites and the liver, thereby improving the condition of HIRI. For example, studies have shown that metformin can alleviate HIRI by inhibiting ferroptosis through gut microbiota-derived gamma-aminobutyric acid [135]. This approach unlocks prospects for more targeted interventions to modulate the intricate interplay between the gut microbiome and liver health, particularly in the context of IRI.

Conclusion

In summary, HIRI is a high-risk complication leading to poor prognosis in patients post-LTx, liver injury, and hepatectomy. Developing effective treatment strategies for HIRI could alleviate liver damage and inflammatory responses in a clinical setting, thus enhancing patient survival rates. Although the discovery of the gut-liver axis presents a new research direction, it is faced with several shortcomings. Firstly, there is a dearth of animal experiments and clinical research linking gut microbiota and metabolic products with HIRI in the gut-liver axis. Secondly, while existing evidence suggests that modulating the gut microbiota helps to alleviate IRI post-LTx or hepatectomy, for instance, by eliminating gut bacteria, abolishing TLR4 signaling, and using remote ischemic preconditioning, the cellular and molecular signaling pathways involved are not fully elucidated. Therefore, developing animal experiments to explore the involved cytokine networks will provide a theoretical basis for future modulation of gut microbiota and its metabolites to mitigate HIRI. Lastly, similar to other liver diseases, the treatment outcomes for HIRI focus on reducing inflammatory responses and minimizing liver damage. However, post-LTx liver IRI involves interactions between the transplant donor and recipient, which may lead to ACR, unlike in acute liver injury from hepatectomy. Studies have reported significant effects of modulating gut microbiota and metabolic products in treating liver diseases, such as cancer, steatohepatitis, and acute liver injury, with antibiotics, prebiotics, probiotics, immunosuppressants, targeted drugs, and fecal microbiota transplantation. Similarly, whether these therapeutic strategies can be applied to HIRI is worthy of investigation. Overall, more animal experiments and clinical studies are needed to validate the mechanisms by which modulation of the gut-liver axis, specifically gut microbiota and metabolic products,

can alleviate HIRI. This may provide better clinical treatment strategies, thereby reducing the mortality rate of patients with HIRI.

Abbreviations

LTx, liver transplantation; IRI, ischemia-reperfusion injury; HIRI, hepatic ischemia-reperfusion injury; BAs, bile acids; ACR, acute cellular rejection; Tregs, regulatory T cells; SCFAs, short-chain fatty acids; LPS, lipopolysaccharides; HMGB1, High Mobility Group Box 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IL-1α and β, interleukins 1α and β; TNF-α and β, tumor necrosis factors α and β; ROS, reactive oxygen species; DAMPs, damage-associated molecular patterns; KCs, Kupffer cells; IPC, ischemic preconditioning; RIPC, remote ischemic preconditioning; HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion; HCC, hepatocellular carcinoma; Th17 cells, T helper 17 cells; MAMPs, microbe-associated molecular patterns; TLR9, Toll-like receptor 9; GPR41, G protein-coupled receptors 41; HDAC, histone deacetylase; MPO, myeloperoxidase; MDA, malondialdehyde; SOCS-3, cytokine signaling inhibitor 3; IRAK-M, interleukin-1 receptor-associated kinase M; JNK, c-Jun N-terminal kinase; ATF4-CHOP, activation transcription factor 4-CCAAT/enhancer-binding protein homologous protein; PERK, protein kinase RNA-like endoplasmic reticulum kinase; caspase-12, Cysteine-aspartic acid protease 12; ATF 6, activating transcription factor 6; IRE-1, inositol-requiring enzyme 1; MAPK, mitogen-activated protein kinase; PMB, polymyxin B; FXR, farnesoid X receptor; TGR5, G protein-coupled receptor 5; CXCL16, C-X-C motif ligand 16; NKT cells, natural killer T cells; LSECs, liver sinusoidal endothelial cells; ABP, Antibiotic Preconditioning; D-Gal, D-galactose; FMT, Fecal Microbiota Transplantation; NASH, non-alcoholic steatohepatitis.

Availability of Data and Materials

Above Graphics are listed within this article and are available upon reasonable request via BioRender.com.

Author Contributions

Conception and design of the work: JW, YY, XD, DZ and PT; funding: DZ and PT; JW, YY wrote the manuscript; JX, XW, HM and QF produced the figures and tables; JW, PT, XW, HM and DZ revised the manuscript. All authors contributed significantly to editorial changes of important content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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